Regulator… Thinking…

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Q. 2.1 To what extent do we ask for NC studies in relevant species, given that the relevant species is often monkey (Limited animals/group).

- The information requested needs to be relevant otherwise is/should not be asked.

- If a monkey study is anticipated not to be informative it should not be required.

- Alternatives (eg other models, in vitro, tissue cross reactivity), may be considered and may even be more informative.

- a thorough justification for the model used should in any case be present.

Q 2.2 How could pharmacodynamic measures ("fingerprinting") be supplementary to quality development?

Comment:

- **PD and Quality are interrelated!**

  when relevant differences are identified in eg
  - receptor-target interaction;
    - Potency, Emax, binding site
  - off targeting characteristics
  - cellular cascades

These may reveal relevant quality differences (then non-similarity)

Q. 2.3 For antitumoural mAbs, to what level would a comparison on the functional level beside ADCC/CDC (if relevant) be required?

What level is feasible (e.g. signalling events)?

Comment:

- The level of feasibility is dictated by the approaches taken for previous characterisation of the reference, taking into consideration the relevance for the biosimilarity exercise.

- Need to be discussed on the basis of feasibility and need.

Q. 2.4 What is the impact of formulation on in vivo behaviour (injection site and infusion rate comparability)? How could it best be studied?

Comment:

- Impact may be:
  - **Local (safety)**
    - **Site of application dependent (test local tolerance)**
    - **Vehicle dependent (test local tolerance)**
  - **Systemic**
    - **Different kinetics**
    - **Enhanced activity**
    - **Altered activity(?)**
    - **Modified immunogenicity (?)**
  - **To be addressed in a Combined PD/PK/safety study (if feasible and relevant?)**

My Question:

- What if non similarity is concluded but the MOA is the same and the basic molecule also (eg different glicosylation pattern)?

How to decide on NHP DART studies for the non-similar when there is experience with the originator?